SLC7A11 Overexpression in Glioblastoma Is Associated with Increased Cancer Stem Cell-Like Properties.

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Public Summary:

Scientific Abstract:
System xc(-) is a sodium-independent electroneutral transporter, comprising a catalytic subunit xCT (SLC7A11), which is involved in importing cystine. Certain cancers such as gliomas upregulate the expression of system xc(-), which confers a survival advantage against the detrimental effects of reactive oxygen species (ROS) by increasing generation of the antioxidant glutathione. However, ROS have also been shown to function as targeted, intracellular second messengers in an array of physiological processes such as proliferation. Several studies have implicated ROS in important cancer features such as migration, invasion, and contribution to a cancer stem cell (CSC)-like phenotype. The role of system xc(-) in regulating these ROS-sensitive processes in glioblastoma multiforme (GBM), the most aggressive malignant primary brain tumor in adults, remains unknown. Stable SLC7A11 knockdown and overexpressing U251 glioma cells were generated and characterized to understand the role of redox and system xc(-) in glioma progression. SLC7A11 knockdown resulted in higher endogenous ROS levels and enhanced invasive properties. On the contrary, overexpression of SLC7A11 resulted in decreased endogenous ROS levels as well as decreased migration and invasion. However, SLC7A11-overexpressing cells displayed actin cytoskeleton changes reminiscent of epithelial-like cells and exhibited an increased CSC-like phenotype. The enhanced CSC-like phenotype may contribute to increased chemoresistance and suggests that overexpression of SLC7A11 in the context of GBM may contribute to tumor progression. These findings have important implications for cancer management where targeting system xC(-) in combination with other chemotherapeutics can reduce cancer resistance and recurrence and improve GBM patient survival.